that binds to an aminophospholipid; and at least a second anti-cancer agent other than said at least a first unconjugated antibody, or antigen-binding fragment thereof.

38. (Amended) In combination, biologically effective amounts of:

(a) a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid;

(b) at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first unconjugated antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid; and

(c) at least a second anti-cancer agent other than said at least a first antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid

Please add new claim 43, as follows:

43. (New) The kit of claim 1, wherein said at least a first pharmaceutically acceptable formulation is a liposomal formulation.

RESPONSE

I. Status of the Claims

Prior to the present Action, claims 1-30 and 34-42 were pending (see **Section III** for discussion of species). Presently, claims 1, 30, 34, and 38 have been amended to even further improve their clarity. No claims have been canceled. Claim 43 has been added, which is fully supported by the application as filed and unified with the examined claims.

Claims 1-30 and 34-43 are therefore in the case. According to 37 C.F.R. § 1.121, and for the convenience of the Examiner, a clean copy of the pending claims is included (**Exhibit A**),

along with a copy of the claims showing the present revisions (**Exhibit B**). The claims in each are marked "(Amended)" or "(New)", where appropriate.

II. Support for the Claims

Support for the amended claims and the new claim is to be found throughout the original application as filed. Any small entity fees necessary for the introduction of the new claim should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4001.002282.

Claim 1 has been revised to even further clarify that the at least a first anti-aminophospholipid antibody, or an antigen-binding fragment thereof, of the claimed kits is "at least a first anti-cancer agent". This is supported throughout the specification, *e.g.*, at least at page 32, lines 7-8. The at least a second anti-cancer agent in claim 1 has also been defined as a second anti-cancer agent "other than" the anti-aminophospholipid antibody or fragment that forms the first anti-cancer agent. This is also supported by the foregoing text in the specification at page 32, with additional support in Section G, where the specification states "each of the anti-aminophospholipid antibody and other anti-cancer agent components of the kit" (specification at page 104, lines 22-24, emphasis added).

Claim 30 has been revised to use the term "said" to better relate each of elements (a), (b) and (c) to claim 1. Although the anti-aminophospholipid antibodies of the claimed kits are "unconjugated" or naked antibodies, the word "unconjugated" has also been removed from claim 30, to better accord with the terminology in claim 1.

In claim 34, the changes are the same as those described above for claim 1 and are similarly supported in the specification.

Elements (b) and (c) of claim 38 have also been revised as described above for claims 1 and 30, which changes are supported by the foregoing sections of the specification.

Finally, claim 43 is a new dependent claim that is supported by original claims 1 and 14 and by the specification, particularly in Section F2, directed to liposomes and nanoparticles (specification at pages 103-104).

It will therefore be understood that no new matter is included within the amended or new claims.

III. Restriction and Species Issues

The Action acknowledges that claims 1-30 and 34-42 are drawn to the elected invention and are pending (Action at Item 2, second sentence). The other statements in the Action, that "claims 2, 13, 15-18, 30, 36-38 are withdrawn from further consideration" and would need to be canceled in reply to a final rejection are therefore in error (Action at Item 2, first sentence, and Item 3).

IV. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

The Action first rejects claims 1, 3-12, 14, 15, 19-29, 34 and 35 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite and for failing to particularly point out and distinctly claim the subject matter of the invention. Although Applicants respectfully traverse, the Action's concerns are addressed.

The Action alleges that the recitation of "at least a second anti-cancer agent" in claims 1, 22, 23, 34 and their dependent claims is ambiguous (Action at Item 7). The Action further takes the position that "the instant claims are not directed to 'naked anti-aminophospholipid antibodies'" (Action at Item 9).

Applicants respectfully point out that all pending claims are, in fact, directed to kits that must comprise a naked anti-aminophospholipid antibody, or antigen-binding fragment thereof, which kits will further comprise at least one of a detectably-labeled antibody that also binds to an aminophospholipid or another anti-cancer agent. Moreover, the Action continues to evidence a clear understanding of the therapeutic kits of the claimed invention (in particular, see Action at page 5, first sentence).

The entire specification, including the text at page 32, is also abundantly clear. In embodiments where the claimed kits comprise an anti-cancer agent "in addition to the naked anti-aminophospholipid antibody", it does not matter whether the naked anti-aminophospholipid antibody or the additional anti-cancer agent is termed the first or second anti-cancer agent.

In any event, claims 1, 30 and 34 have been revised to unambiguously state that the "at least a first anti-cancer agent" is the first antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid, and that the at least a second anti-cancer agent is an anti-cancer agent "other than" the first anti-aminophospholipid antibody or antigen-binding fragment thereof. These clarifications directly address the Action's concern at Item 10.

The rejection under 35 U.S.C. § 112, second paragraph is therefore overcome and should be withdrawn.

V. Rejection of Claims 1, 3-6, 8, 12, 14 and 19 Under 35 U.S.C. § 102(b)

The Action next rejects claims 1, 3-6, 8, 12, 14 and 19 under 35 U.S.C. § 102(b) as allegedly being anticipated by Fishman *et al.*, *Intl. J. Oncol.*, 10:901-904, 1997 ("Fishman"). Although Applicants respectfully traverse, the Action's concerns are addressed.

A rejection on the grounds of anticipation requires the disclosure, in a single reference, of every element of a claimed invention and requires that each and every facet of the claimed invention

be identified in the applied reference. *Ex parte Levy*, 17 USPQ2d 1461 (B.P.A.I. 1990); *Minnesota Mining & Mfg. v. Johnson & Johnson Orthopaedics, Inc.*, 24 USPQ2d 1321 (Fed. Cir. 1992).

Fishman is cited as disclosing "anti-phospholipid antibodies directed to melanoma cells and other the [*sic*] cancer cells having over expressed outer membrane phosphatidylserine" and as "purifying IgG anti-PS antibodies from patients with antiphospholipid syndrome and examining their *in vivo* efficacy against melanoma tumor cells ELISA tests (Action at Item 13, page 5). Fishman more properly concerns various observations on autoimmunity and cancer.

The Action continues to allege that, as apparently argued in Applicants' first response (September, 2001), and in view of the definition of the first and second anti-cancer agents at page 32 of the specification, "it appears that the second anti-cancer agent can be the same as the first anti-cancer agent" (Action at Item 14). Applicants respectfully disagree and, should this interpretation of Applicants' earlier response be maintained, it is respectfully requested that the Office identify the particular section of the response that is being relied upon.

Moreover, the specification at page 32, lines 1-9, does not in any respect indicate that the second anti-cancer agent is the same as the first anti-cancer agent. This paragraph simply explains that it is irrelevant as to which anti-cancer agent is termed "first" or "second", simply for grammatical purposes when reading the specification and claims.

The Action next takes the position that as the first anti-cancer agent in the claimed invention encompasses anti-aminophospholipid antibodies, it is the Examiner's position that "Fishman's separate doses of anti-PS antibodies meets the limitations of the instant claims because they are directed to two separate anti-cancer agents" (Action at Item 14). Applicants have studied the Fishman reference and can find no mention of "separate doses of anti-PS antibodies" as alleged in the Action. Should the Office continue with this line of reasoning,

Applicants respectfully request that the particular portion of Fishman believed to teach separate doses of anti-PS antibodies be identified.

Should the Office intend to take the position that Fishman is "directed to two separate anti-cancer agents" aside from the alleged "separate dose" issue, this would be in contrast to the first Official Action in this application, wherein the Office admitted that Fishman "does not teach the combination of a anti-aminophospholipid [*sic*] antibody with a second anti-cancer agent for therapeutic kits (first Action at page 8, last paragraph). The Office would therefore be advancing a different interpretation of Fishman than earlier set forth on the record and, should such an interpretation be continued, Applicants respectfully request that the particular portion of Fishman relied upon be pointed out.

Finally under this section, the Action assesses Fishman as teaching "the potential use of autoantibodies in diagnostic and therapeutic area [*sic*] such as treatment of squamous cell carcinoma of the skin", and cites Fishman at the Abstract and at page 903, second column, second paragraph (Action at Item 14). Applicants first respectfully point out that the Abstract does not appear to contain any reference to the treatment of squamous cell carcinoma of skin. More importantly, the references in Fishman to squamous cell carcinoma treatment are totally separate from anti-PS antibodies, and rather concern anti-keratinocyte antibodies (Fishman at Table I, last line; page 903, second column, paragraph beginning "b)").

In summary, the instant specification and claims make it clear that the kits of the invention contain two distinct anti-cancer agents, one of which is an anti-aminophospholipid antibody. Fishman does not teach the combination of an anti-aminophospholipid antibody with a second anti-cancer agent, as acknowledged in the first Official Action at page 8. Fishman also fails to teach or suggest an anti-aminophospholipid antibody in conjunction with a detectably

labeled antibody that also binds to an aminophospholipid. Fishman thus clearly fails to anticipate the claimed invention. *Minnesota Mining & Mfg., supra.*

The rejection under 35 U.S.C. § 102(b) over Fishman is therefore overcome and should be withdrawn.

VI. Rejection of Claims 1, 3-12, 14, 19-22 and 39-42 Under 35 U.S.C. § 102(e)

The Action next rejects claims 1, 3-12, 14, 19-22 and 39-42 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,300,308 to Schroit ("Schroit"). Although Applicants respectfully traverse, the Action's concerns are addressed.

The Action at Item 15 rejects claims 1, 3-12, 14, 19-22 and 39-42 over Schroit, which is first cited as disclosing "methods for inhibiting cancer cell growth or killing cancer cells comprising eliciting a lipid specific antibody response with an immunologically effective amount of composition comprising a phophatidylserine/polypetptide [*sic*] conjugate" (Action at page 6, first sentence).

As the presently claimed invention is not drawn to methods, but to kits comprising a naked anti-aminophospholipid antibody and either a detectably-labeled anti-aminophospholipid antibody or a second anti-cancer agent, the methods of Schroit are not relevant to a rejection under § 102(e). The phosphatidylserine-polypeptide conjugates for use in the Schroit methods are not pertinent to the rejection, as the claimed components of the present kits are not phosphatidylserine-polypeptide conjugates.

The Action at page 6 continues to describe Schroit as disclosing "kits comprising a lipid or lipid-carrier conjugate antigen-specific antibodies with suitable immunodetecting reagents such as detectable labels linked to a protein, peptide or antibody directed to aminophospholipid receptors in suitable pharmaceutical formulations", and cites Schroit at column 6, lines 65-68,

column 7, lines 13-35, "example" and column 23, lines 29-65. The Action's reference to an antibody directed to "aminophospholipid receptors" is not understood, and Applicants respectfully request clarification of this terminology and the intended meaning.

Schroit at column 6, line 65 to column 7, line 3 and at column 7, lines 13-35 (in part) concerns immunodetection kits and methods using immunodetection reagents alone. Although the immunodetection can be achieved using a first, labeled antibody (column 6) or a second labeled antibody (column 7, lines 1-3)[1], there is no reference to any therapeutic agent in the Schroit kits at columns 6 and 7. Schroit at columns 6 and 7 also lacks any reference to "pharmaceutical formulations", and the Action is therefore in error in this assessment of Schroit.

In contrast to the immunodetection kits of Schroit, the detectably-labeled anti-aminophospholipid antibodies encompassed within the kits of the present invention are always present in combination with a therapeutic antibody, *i.e.*, the naked or unconjugated anti-aminophospholipid antibody recited in the kits. Thus, the section of Schroit from column 6, line 65 to column 7, line 3 is not relevant to an anticipation rejection as it lacks a key feature of the claimed invention, namely the therapeutic antibody. *Minnesota Mining & Mfg., supra.*

The next quoted section of Schroit, column 23, lines 29-65, concerns the preparation of PS-carrier conjugates and the production of antisera from rabbits immunized against PS-BSA. This section of Schroit is not germane to the claimed invention, *i.e.*, to kits containing a naked anti-aminophospholipid antibody in combination with a second anti-cancer agent or a detectably-labeled anti-aminophospholipid antibody, and does not support the § 102(e) rejection.

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[1] Although column 7 mentions in passing that antibodies can be used in detection, the emphasis of column 7 concerns the use of a lipid and/or lipid conjugate in detection, which is not relevant to the claimed invention.

The Action next states, "Schroit sets forth that his PS-specific antibodies can be used in for [*sic*] prevention and treatment of conditions such as cancer wherein surfaces of the cells causing the condition are characterized by the presence of PS on their external leaflet" and cites Schroit at column 16, lines 38-44 and column 19, lines 36-67 (Action at page 6, third sentence).

Applicants have studied Schroit at column 16, lines 38-44 and column 19, lines 36-67 and cannot find a disclosure that teaches or suggests the presently claimed kits of naked anti-aminophospholipid antibodies in combination with a second anti-cancer agent or a detectably-labeled anti-aminophospholipid antibody.

The § 102(e) rejection at Item 15 is therefore overcome and should be withdrawn.

The Action continues with the § 102(e) rejection over Schroit at Item 16, stating "Schroit also discloses therapeutic kits comprising one or more lipid conjugate antigens or antibodies directed to phosphatidylserine receptors[2] in separate containers" (col 7, lines 40-67; col 8, lines 1-40; col 28, lines 1-67); subsequently, the kits of Schroit contain at least two anticancer agents" (Action at Item 16, page 6; emphasis added). The Action's assessment of Schroit, and the resultant § 102(e) rejection, are in error. To the extent that Schroit concerns kits with "distinct container means" (Schroit at column 7, line 66), Schroit states:

> "In such cases, one or more containers would contain each of the PS composition(s), either as sterile solutions, powders, lyophilized forms, etc., and the other container(s) would include a matrix, solution, or other suitable delivery device for applying the composition to the body, bloodstream, or to a tissue site, skin lesion, tumor cell, wound area, or other site of administration. Such delivery device may or may not itself contain a sterile solution, diluent, gelatinous matrix, carrier or other pharmaceutically-acceptable components. The kits may also comprise a second or third container means for containing a sterile, pharmaceutically acceptable buffer, diluent or solvent".

Schroit at column 7, line 66 to column 8, line 11; emphases added.

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[2] The reference to antibodies directed to "phosphatidylserine receptors" is not understood, and Applicants again respectfully request clarification from the Office.

Thus, the Action wrongly concludes that Schroit discloses one or more lipid conjugate antigens or antibodies directed to phosphatidylserine receptors in separate containers. As shown above, the "other container(s)" of Schroit include either a delivery device for application to the body or a pharmaceutically acceptable buffer. The quoted section at column 28, lines 1-67 does not support the Action's position, as this simply describes the generation of phosphatidylserine/ phosphatidylcholine β2-glycoprotein I conjugates and the immunization of mice prior to inoculation with tumor cells. Combination kits are not disclosed at column 28.

Even assuming, *arguendo*, that Schroit at columns 7, 8 and/or 28 disclosed one or more antibodies directed to phosphatidylserine in separate containers, as suggested in the Action, this does support the Action's conclusion that Schroit anticipates the claimed invention. The therapeutic kits of the present invention are not simply kits containing one or more anti-phosphatidylserine antibodies in separate containers, but kits containing at least a first naked antibody that binds to an aminophospholipid in combination with at least a second, distinct anti-cancer agent, *i.e.*, another anti-cancer agent other than the anti-aminophospholipid antibody (specification at page 104, lines 22-24). Thus, even a liberal interpretation of Schroit at columns 7, 8 and/or 28 fails to support the rejection.

The Action next characterizes Schroit as teaching "combination of his antibodies with a secondary anti cancer agents [*sic*] such as diphtheria toxoid", and cites Schroit at column 8, lines 65-67 (Action at page 6). Applicants respectfully point out that the Action has mischaracterized this section of Schroit. Rather than teaching the use of diphtheria toxoid as an anti-cancer agent, Schroit at column 8, lines 58-67 teaches that with respect to preparing lipid-specific antibodies, "it is necessary to boost the host immune system", which may be achieved by coupling the lipid of interest to a carrier. Diphtheria toxoid is set forth as one example of such a

carrier, along with KLH, BSA, β2-glycoprotein I, albumins such as ovalbumin, mouse serum albumin or rabbit serum albumin, and bovine gamma globulin (Schroit at column 8, lines 58-67). Thus, the diphtheria toxoid of Schroit is a carrier for lipid immunization, not a secondary anti-cancer agent, and Schroit is not anticipatory.

Moreover, diphtheria toxoid is not included within the scope of the present claims as a carrier for immunization, because the Schroit "carriers" are conjugated to the "lipid of interest" and the present kits are not concerned with lipids for immunization, but with naked antibodies for use as therapeutics, in combination with other anti-cancer agents or aminophospholipid diagnostic antibodies.

Finally, whether or not Schroit discloses the use of humanized or recombinant antibodies in preparing his compositions (Action at page 6) is not relevant to the present enquiry. As Schroit does not teach or suggest a kit comprising an unconjugated anti-aminophospholipid antibody and either a detectably-labeled anti-aminophospholipid antibody or a second anti-cancer agent other than the naked anti-aminophospholipid antibody, Schroit fails to anticipate the claimed invention irrespective of any discussion of humanized or recombinant antibodies.

Applicants' foregoing response to the reasoning set forth in Action should not be interpreted as acquiescing that the effective filing of date Schroit is earlier than the effective filing date of the present invention. Nor should this be interpreted as Applicants waiving any rights to establish a date of invention earlier than the effective filing date of Schroit.

For at least the above reasons, Schroit is not competent prior art and fails to anticipate the claimed invention. The rejection under 35 U.S.C. § 102(e) over Schroit is thus overcome and should be withdrawn.

VII. Rejection of Claims 23-29, 34 and 35 Under 35 U.S.C. § 103(a)

Claims 23-29, 34 and 35 are further rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over the foregoing Schroit patent in view of U.S. Patent No. 5,632,991 to Gimbrone ("Gimbrone") and Umeda *et al.*, *J. Immunol.*, 143:2273-2279, 1989, ("Umeda"). Although Applicants respectfully traverse, the Action's concerns are addressed.

For an obviousness rejection to be proper under 35 U.S.C. § 103(a), it is required that the cited prior art suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and that the prior art also convey to those of ordinary skill a reasonable expectation of success. *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

When, as in the present case, an obviousness rejection depends on a combination of prior art references, there must be some teaching, suggestion or motivation to combine the references. *In re Rouffet*, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998). Even if every element of an invention can be found in the prior art, obviousness is not established in the absence of sufficient "motivation to combine". *Rouffet* at 1457-1458. A high level of skill in the art cannot be held to substitute for the required motivation to combine. *Rouffet* at 1458.

Properly combined references, even if providing some suggestion towards the invention, are insufficient to establish legal obviousness unless they also provide "a reasonable expectation of success". *In re Dow Chemical Co., supra; In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

The Action states that Schroit "fails to specifically disclose the use of other suitable antiphospholipid antibodies in combination with an anti-cancer agent conjugated to a targeting antibody" (Action at Item 18, bridging pages 7 and 8). As detailed above (**Section VI**), Schroit in fact fails to teach or suggest the use of a kit comprising a naked anti-aminophospholipid antibody in combination with any anti-cancer agent. Schroit therefore fails to teach or suggest any kits of relevance to the present invention. The admitted failure to disclose additional anti-cancer agents in the form of antibody-therapeutic agent constructs is just one particular omission in Schroit.

Gimbrone is first cited as disclosing "targeting agents conjugated to an antibody directed to ELAM-1 (E-selectin)" (Action at Item 19, page 8). The Action has yet to clarify the meaning of "targeting agents conjugated to an antibody", as requested earlier, and Applicants again respectfully request that the Office explain the intended meaning. The Action next states, "Gimbrone teaches that such endothelial specific adhesion molecules are rapidly unregulated on the surface of cultured human vascular endothelial cells (Action at page 9; emphasis added). Applicants cannot discern the relevance of the stated presence of unregulated endothelial specific adhesion molecules on cultured human vascular endothelial cells to the present invention, and appropriate clarification is respectfully requested.

The Action at page 8, further states, "Gimbrone also discloses the use of his targeting agent-therapeutic agent conjugate, alone or in combination with other antibody or antibody fragment and/or a therapeutic agent (a second anti-cancer agent)" and cites Gimbrone at column 15, lines 46-55 (Action at page 8). As pointed out in Applicants' first response, even if this assessment of Gimbrone was accurate, the present invention is not directed to E-selectin targeting agent-therapeutic agent conjugates, but to kits comprising naked antibodies against

aminophospholipids in combination with either a detectably-labeled anti-aminophospholipid antibody or a second anti-cancer agent.

In any event, the Action's assessment of Gimbrone is in error. Gimbrone at column 15, lines 46-55 does not disclose an E-selectin targeting agent-therapeutic agent conjugate "in combination with other antibody or antibody fragment and/or a therapeutic agent (a second anti-cancer agent)". Rather, this section of Gimbrone is entirely limited to the use of an "E-selectin specific monoclonal antibody, or antibody fragment" (Gimbrone at column 15, lines 43-44) or an "E-selectin specific monoclonal antibody [is] conjugated to an anti-inflammatory agent, anti-thrombotic agent, anti-complement agent, or immunosuppressive agent" (Gimbrone at column 15, lines 49-52), each of which are used alone, not in combination.

Gimbrone at column 15, lines 46-55 therefore does not mention a kit comprising an E-selectin antibody or antibody conjugate in combination with any second therapeutic agent, let alone a second anti-cancer agent. Gimbrone particularly lacks any teaching or suggestion of a kit comprising an anti-E-selectin antibody conjugate in combination with a naked antibody that binds to an aminophospholipid (as later acknowledged in the Action at page 8).

The Action next takes the position that the "therapeutic agents of Gimbrone produce apoptosis as they encompass various toxins, antioxidants and anti-tumor drugs", citing Gimbrone at columns 12-14 and claim 2 (Action at page 8). As cleared recited in claims 1 and 2 of Gimbrone, this teaching is entirely confined to immunoconjugates comprising the anti-E-selectin antibody, H18/7, conjugated to a therapeutic agent. Equally, Gimbrone at columns 12-14 is limited to the use of anti-E-selectin antibodies alone or anti-E-selectin antibody conjugates alone. Gimbrone at columns 12-14 does not suggest an anti-E-selectin antibody conjugate in combination with any distinct toxin, antioxidant or anti-tumor drug, and is far removed from

suggesting combination with a naked antibody that binds to an aminophospholipid (as acknowledged in the Action at page 8).

Gimbrone at column 13, lines 58-67 is further said to teach that E-selectin or a leukocyte binding fragment thereof can be coupled to a chemotherapeutic drug that binds to tumor cells expressing receptors for E-selectin, to kill the tumor cells (Action at page 8). Again, this reference is limited to the use of a single therapeutic conjugate, and does not include any suggestion of combinations with second anti-cancer agents, particularly not combinations with naked antibodies that bind to aminophospholipids (acknowledged in the Action at page 8).

Thus, Gimbrone is entirely limited to suggestions for using various single therapeutic agents based upon E-selectin or anti-E-selectin antibodies or conjugates thereof. As agreed, Gimbrone does not teach or suggest any combination therapies with anti-aminophospholipid antibodies (acknowledged in the Action at page 8). Schroit concerns lipid-carrier protein conjugate compositions for generating lipid-specific immune responses in an animal (Schroit at abstract). Schroit does not concern E-selectin or anti-E-selectin antibodies or conjugates, and does not teach or suggest any combination therapies with E-selectin-based therapeutics.

Before the P.T.O. may combine the disclosure of two or more prior art references in order to establish *prima facie* obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of skill in the art. *In re Fine*, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988). As Gimbrone does not concern lipid-carrier protein conjugates, lipid-specific immune responses, aminophospholipids or anti-aminophospholipid antibodies, and Schroit does not concern E-selectin, anti-E-selectin antibodies, antibody conjugates or therapeutic methods based upon E-selectin, the references have been improperly combined.

As to diagnostic kits, the Action characterizes Gimbrone as disclosing methods for detecting E-selectin expression within the body of a patient comprising steps of detecting E-selectin by labeling the E-selectin antibody with a radioactive isotope that can be detected, citing Gimbrone at column 18, lines 60-65 (Action at page 8).

This is particularly far removed from the present invention, as the diagnostic embodiments within the claimed kits require a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid, in combination with the therapeutic antibody that binds to an aminophospholipid. Radioactively labeled anti-E-selectin antibodies have absolutely no relevance to the claimed invention.

As to the third reference in the combination, Umeda is first cited as teaching "methods of producing monoclonal antibodies directed to phosphatidylserine of plasma membrane and that patients with malignancy have a higher titer of anti-PS antibodies" (Action at Item 20, bridging pages 8 and 9). The Action continues, "Umeda's teachings are used to show the conventional practice of preparing monoclonal antibodies directed to phosphatidylserine of outer cell membrane. Umeda does not teach the use of his antibodies in kits for diagnostic or therapeutic purposes" (Action at page 9; emphasis added).

As Umeda does not teach the use of antibodies to aminophospholipids in kits for diagnostic or therapeutic purposes, and as directly stated in the Action, Umeda is cited for the purpose of showing conventional technical skill in the art. Any attempt to show that an invention is within the level of ordinary skill in the art is misplaced in an obviousness rejection. In overturning two § 103(a) rejections as improperly relying on the high level of skill in the art, the Federal Circuit held:

> "The Board merely invoked the high level of skill in the field of the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness".
>
> *Rouffet* at 1456.

The Action next alleges that the teachings of Schroit, Gimbrone and Umeda are in the same field of endeavor as they are all directed to the field of antibody immunology (Action at Item 21, page 9). Such a position can only be reached by a significant extrapolation of each reference. More properly, Schroit concerns lipid-carrier protein conjugate compositions for generating lipid-specific immune responses, Gimbrone concerns E-selectin, anti-E-selectin antibodies and immunoconjugates and Umeda concerns stereo-specific recognition of phosphatidylserine by monoclonal antibody. In any event, even if Schroit, Gimbrone and Umeda are all directed to the field of antibody immunology, the field of the present invention, as described in the opening sentence of the application, is the field of blood vessels and tumor biology.

Moreover, even if Schroit, Gimbrone and Umeda are properly combined, these references in combination still fail to teach or suggest the kits of the claimed invention, drawn to a naked anti-aminophospholipid antibody and either a detectably-labeled anti-aminophospholipid antibody or a second anti-cancer agent. The references in combination further fail to provide the reasonable expectation of success required to render the invention unpatentable.

The first rejection under 35 U.S.C. § 103(a) is thus overcome and should be withdrawn.

VIII. Rejection of Claims 7, 9-11, 20-29, 34, 35 and 39-42 Under 35 U.S.C. § 103(a)

Lastly, the Action rejects claims 7, 9-11, 20-29, 34, 35 and 39-42 under 35 U.S.C. § 103(a) as allegedly being legally obvious over the foregoing Fishman reference in view of U.S. Patent No. 5,658,570 to Newman ("Newman") in further view of the foregoing Gimbrone patent. Although Applicants respectfully traverse, the Action's concerns are addressed.

The Action refers to Fishman as discussed above, but acknowledges that Fishman fails to disclose the use of humanized or other suitable antibodies "in combination with an anti-cancer agent conjugated to a targeting antibody" (Action at Item 24). As detailed above (**Section V**), Fishman does not in fact teach or suggest the use of an anti-aminophospholipid antibody in combination with any anti-cancer agent, as acknowledged in the first Official Action (see first Action at page 8). Fishman therefore fails to teach or suggest a kit in accordance with the claimed invention.

Newman is cited as teaching methods of preparing humanized antibodies directed against certain human receptor antigens, such as ELAM, VCAM, TFGα, *etc.* for therapeutic administration (Action at Item 25). Newman in fact concerns chimeric antibodies comprising a human or chimpanzee constant region and an antigen-binding region from an old world monkey (Newman at Abstract, claims). The Action readily acknowledges that Newman does not teach humanized antibodies directed against aminophospholipids (Action at Item 25).

As Newman does not concern antibodies against aminophospholipids or kits comprising combinations of anti-cancer agents, and as the present claims do not recite antibodies with antigen binding regions from old world monkeys, a proper combination has not been established, either between Newman and Fishman or between Newman and the claimed invention.

The Action at Item 27, page 11, indicates that the teachings of Fishman, Newman and Gimbrone are in the same field of endeavor, as they are all directed to the field of antibody immunology. Again, this requires both extrapolation of the references and dismissal of their most pertinent features. More properly, Fishman provides observations on autoimmunity and cancer, Newman concerns chimeric antibodies using old world monkey antigen-binding regions, and Gimbrone concerns E-selectin, anti-E-selectin antibodies and immunoconjugates.

Even if Fishman, Newman and Gimbrone were all considered to be in field of antibody immunology, the field of the present invention is the field of blood vessels and tumor biology. Applicants have studied Fishman, Newman and Gimbrone and can find no reference in any of these references to tumor blood vessels, aminophospholipids as markers of tumor blood vessels, or combinations of naked anti-aminophospholipid antibodies with different anti-cancer agents and/or aminophospholipid diagnostics.

Importantly, even if combined, Fishman, Newman and Gimbrone fail to teach or suggest a kit comprising an unconjugated anti-aminophospholipid antibody in combination with a second, distinct anti-cancer agent or a detectably-labeled antibody that binds to an aminophospholipid.

The second § 103(a) rejection is therefore overcome and should be withdrawn.

IX. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks and enclosed documents, the present case is in condition for allowance and such favorable action is respectfully requested.

Should Examiner Sharareh have any questions or comments, or identify any informalities, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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EXHIBIT A
PENDING CLAIMS
U.S. Serial No. 09/351,862 (4001.002282; UTSD:549--1)

1. (Amended) A kit comprising, in a pharmaceutically acceptable form, biologically effective amounts of at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid; and:

(a) a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid; or

(b) at least a second anti-cancer agent other than said at least a first antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid.

2. The kit of claim 1, wherein said kit comprises at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylethanolamine.

3. The kit of claim 1, wherein said kit comprises at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylserine.

4. The kit of claim 1, wherein said kit comprises at least a first IgG or IgM antibody that binds to an aminophospholipid.

5. The kit of claim 1, wherein said kit comprises at least a first scFv, Fv, Fab', Fab or $F(ab')_2$ antigen-binding fragment of an antibody that binds to an aminophospholipid.

6. The kit of claim 1, wherein said kit comprises at least a first monoclonal antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

7. The kit of claim 1, wherein said kit comprises at least a first recombinant antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

8. The kit of claim 1, wherein said kit comprises at least a first human, humanized or part-human chimeric antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

9. The kit of claim 8, wherein said kit comprises at least a first antibody comprising a mouse antibody variable region that binds to an aminophospholipid operatively attached to a human antibody framework or constant region.

10. The kit of claim 8, wherein said kit comprises at least a first recombinant, human antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

11. The kit of claim 1, wherein said kit comprises at least a first dimer, trimer or multimer of an antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

12. The kit of claim 1, wherein said kit comprises at least a first and second antibody, or antigen-binding fragments thereof, that bind to an aminophospholipid.

13. The kit of claim 12, wherein said kit comprises at least a first antibody, or antigen-binding fragment thereof, that binds to phosphatidylethanolamine and at least a second antibody, or antigen-binding fragment thereof, that binds to phosphatidylserine.

14. The kit of claim 1, wherein said kit comprises at least a first pharmaceutically acceptable formulation suitable for intravenous administration.

15. The kit of claim 1, wherein said kit comprises, in distinct pharmaceutical compositions, said at least a first antibody, or antigen-binding fragment thereof, and said detectably-labeled antibody, or antigen-binding fragment thereof.

16. The kit of claim 15, wherein said detectably-labeled antibody, or antigen-binding fragment thereof, comprises the X-ray detectable compound bismuth (III), gold (III), lanthanum (III) or lead (II).

17. The kit of claim 15, wherein said detectably-labeled antibody, or antigen-binding fragment thereof, comprises the detectable radioactive ion copper^{67}, gallium^{67}, gallium^{68}, indium^{111}, indium^{113}, iodine^{123}, iodine^{125}, iodine^{131}, mercury^{197}, mercury^{203}, rhenium^{186}, rhenium^{188}, rubidium^{97}, rubidium^{103}, technetium^{99m} or yttrium^{90}.

18. The kit of claim 15, wherein said detectably-labeled antibody, or antigen-binding fragment thereof, comprises the detectable nuclear magnetic spin-resonance isotope cobalt (II), copper (II), chromium (III), dysprosium (III), erbium (III), gadolinium (III), holmium (III), iron (II), iron (III), manganese (II), neodymium (III), nickel (II), samarium (III), terbium (III), vanadium (II) or ytterbium (III).

19. The kit of claim 1, wherein said kit comprises said at least a first antibody, or antigen-binding fragment thereof, and said at least a second anti-cancer agent.

20. The kit of claim 19, wherein said at least a first antibody, or antigen-binding fragment thereof, and said at least a second anti-cancer agent are comprised within a single pharmaceutical composition.

21. The kit of claim 19, wherein said at least a first antibody, or antigen-binding fragment thereof, and said at least a second anti-cancer agent are comprised within distinct pharmaceutical compositions.

22. The kit of claim 19, wherein said at least a second anti-cancer agent is a chemotherapeutic agent, radiotherapeutic agent, anti-angiogenic agent or apoptosis-inducing agent.

23. The kit of claim 19, wherein said at least a second anti-cancer agent is an antibody-therapeutic agent construct comprising a targeting antibody, or antigen-binding fragment thereof, that binds to a surface-expressed, surface-accessible or surface-localized component of a tumor cell, tumor stroma or tumor vasculature; wherein said targeting antibody or fragment thereof is operatively linked to a therapeutic agent.

24. The kit of claim 23, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a surface-expressed, surface-accessible, surface-localized, cytokine-inducible or coagulant-inducible component of intratumoral blood vessels of a vascularized tumor.

25. The kit of claim 24, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a surface-expressed component of intratumoral vasculature selected from the group consisting of an aminophospholipid, endoglin, a TGFβ receptor, E-selectin, P-selectin, VCAM-1, ICAM-1, PSMA, a VEGF/VPF receptor, an FGF receptor, a TIE, $\alpha_v\beta_3$ integrin, pleiotropin, endosialin and an MHC Class II protein.

26. The kit of claim 24, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a surface-localized component of intratumoral vasculature selected from the group consisting of VEGF/VPF, FGF, TGFβ, a ligand that binds to a TIE, a tumor-associated fibronectin isoform, scatter factor/hepatocyte growth factor (HGF), platelet factor 4 (PF4), PDGF and TIMP.

27. The kit of claim 23, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to a cytotoxic agent.

28. The kit of claim 23, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to a coagulation factor or to an antibody, or antigen-binding fragment thereof, that binds to a coagulation factor.

29. The kit of claim 23, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to deglycosylated ricin A chain, Tissue Factor, truncated Tissue Factor or to an antibody, or antigen-binding fragment thereof, that binds to Tissue Factor or truncated Tissue Factor.

30. (Amended) The kit of claim 1, wherein said kit comprises biologically effective amounts of:

(a) said detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid;

(b) said at least a first antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid; and

(c) said at least a second anti-cancer agent.

34. (Amended) A therapeutic kit comprising, in at least a first suitable container, a combined pharmaceutically effective amount of at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first unconjugated antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid; and at least a second anti-cancer agent other than said at least a first unconjugated antibody, or antigen-binding fragment thereof.

35. The kit of claim 34, wherein said at least a second anti-cancer agent is an anti-angiogenic agent, apoptosis-inducing agent or a vascular targeting agent.

36. The kit of claim 34, wherein said kit further comprises a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

37. A medicinal cocktail comprising, in a pharmaceutically acceptable form, a combined effective amount of at least a first anti-cancer agent and at least a first unconjugated antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid.

38. (Amended) In combination, biologically effective amounts of:

(a) a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid;

(b) at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first unconjugated antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid; and

(c) at least a second anti-cancer agent other than said at least a first antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid.

39. A kit comprising at least a first antibody that binds to an aminophospholipid on the luminal surface of tumor vascular endothelial cells in an amount effective to kill at least a portion of said tumor vascular endothelial cells upon administration to an animal with a vascularized tumor; said kit further comprising:

(a) a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid; or

(b) an anti-cancer agent.

40. A kit comprising at least a first antibody that binds to an aminophospholipid on the luminal surface of tumor vascular endothelial cells in an amount effective to induce cell death in at least a portion of said tumor vascular endothelial cells upon administration to an animal with a vascularized tumor; said kit further comprising:

(a) a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid; or

(b) a therapeutically effective amount of an anti-cancer agent.

41. A kit comprising at least a first antibody that binds to an aminophospholipid on the luminal surface of tumor vascular endothelial cells in an amount effective to effective to occlude or destroy at least a portion of tumor blood vessels upon administration to an animal with a vascularized tumor; said kit further comprising:

(a) a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding region thereof, that binds to an aminophospholipid; or

(b) a therapeutically effective amount of an anti-cancer agent.

42. A kit comprising at least a first antibody that binds to an aminophospholipid on the luminal surface of tumor vascular endothelial cells in an amount effective to induce tumor necrosis, tumor regression or tumor destruction upon administration to an animal with a vascularized tumor; said kit further comprising:

(a) a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding region thereof, that binds to an aminophospholipid; or

(b) a therapeutically effective amount of an anti-cancer agent.

43. (New) The kit of claim 1, wherein said at least a first pharmaceutically acceptable formulation is a liposomal formulation.

EXHIBIT B
PENDING CLAIMS
U.S. Serial No. 09/351,862 (4001.002282; UTSD:549--1)

1. (Amended) A kit comprising, in a pharmaceutically acceptable form, biologically effective amounts of at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid; and:

(a) a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid; or

(b) at least a second anti-cancer agent other than said at least a first antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid.

2. The kit of claim 1, wherein said kit comprises at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylethanolamine.

3. The kit of claim 1, wherein said kit comprises at least a first antibody, or antigen-binding fragment thereof, binds to phosphatidylserine.

4. The kit of claim 1, wherein said kit comprises at least a first IgG or IgM antibody that binds to an aminophospholipid.

5. The kit of claim 1, wherein said kit comprises at least a first scFv, Fv, Fab', Fab or $F(ab')_2$ antigen-binding fragment of an antibody that binds to an aminophospholipid.

6. The kit of claim 1, wherein said kit comprises at least a first monoclonal antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

7. The kit of claim 1, wherein said kit comprises at least a first recombinant antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

8. The kit of claim 1, wherein said kit comprises at least a first human, humanized or part-human chimeric antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

9. The kit of claim 8, wherein said kit comprises at least a first antibody comprising a mouse antibody variable region that binds to an aminophospholipid operatively attached to a human antibody framework or constant region.

10. The kit of claim 8, wherein said kit comprises at least a first recombinant, human antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

11. The kit of claim 1, wherein said kit comprises at least a first dimer, trimer or multimer of an antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

12. The kit of claim 1, wherein said kit comprises at least a first and second antibody, or antigen-binding fragments thereof, that bind to an aminophospholipid.

13. The kit of claim 12, wherein said kit comprises at least a first antibody, or antigen-binding fragment thereof, that binds to phosphatidylethanolamine and at least a second antibody, or antigen-binding fragment thereof, that binds to phosphatidylserine.

14. The kit of claim 1, wherein said kit comprises at least a first pharmaceutically acceptable formulation suitable for intravenous administration.

15. The kit of claim 1, wherein said kit comprises, in distinct pharmaceutical compositions, said at least a first antibody, or antigen-binding fragment thereof, and said detectably-labeled antibody, or antigen-binding fragment thereof.

16. The kit of claim 15, wherein said detectably-labeled antibody, or antigen-binding fragment thereof, comprises the X-ray detectable compound bismuth (III), gold (III), lanthanum (III) or lead (II).

17. The kit of claim 15, wherein said detectably-labeled antibody, or antigen-binding fragment thereof, comprises the detectable radioactive ion copper^{67}, gallium^{67}, gallium^{68}, indium^{111}, indium^{113}, iodine^{123}, iodine^{125}, iodine^{131}, mercury^{197}, mercury^{203}, rhenium^{186}, rhenium^{188}, rubidium^{97}, rubidium^{103}, technetium^{99m} or yttrium^{90}.

18. The kit of claim 15, wherein said detectably-labeled antibody, or antigen-binding fragment thereof, comprises the detectable nuclear magnetic spin-resonance isotope cobalt (II), copper (II), chromium (III), dysprosium (III), erbium (III), gadolinium (III), holmium (III), iron (II), iron (III), manganese (II), neodymium (III), nickel (II), samarium (III), terbium (III), vanadium (II) or ytterbium (III).

19. The kit of claim 1, wherein said kit comprises said at least a first antibody, or antigen-binding fragment thereof, and said at least a second anti-cancer agent.

20. The kit of claim 19, wherein said at least a first antibody, or antigen-binding fragment thereof, and said at least a second anti-cancer agent are comprised within a single pharmaceutical composition.

21. The kit of claim 19, wherein said at least a first antibody, or antigen-binding fragment thereof, and said at least a second anti-cancer agent are comprised within distinct pharmaceutical compositions.

22. The kit of claim 19, wherein said at least a second anti-cancer agent is a chemotherapeutic agent, radiotherapeutic agent, anti-angiogenic agent or apoptosis-inducing agent.

23. The kit of claim 19, wherein said at least a second anti-cancer agent is an antibody-therapeutic agent construct comprising a targeting antibody, or antigen-binding fragment thereof, that binds to a surface-expressed, surface-accessible or surface-localized component of a tumor cell, tumor stroma or tumor vasculature; wherein said targeting antibody or fragment thereof is operatively linked to a therapeutic agent.

24. The kit of claim 23, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a surface-expressed, surface-accessible, surface-localized, cytokine-inducible or coagulant-inducible component of intratumoral blood vessels of a vascularized tumor.

25. The kit of claim 24, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a surface-expressed component of intratumoral vasculature selected from the group consisting of an aminophospholipid, endoglin, a TGFβ receptor, E-selectin, P-selectin, VCAM-1, ICAM-1, PSMA, a VEGF/VPF receptor, an FGF receptor, a TIE, $\alpha_v\beta_3$ integrin, pleiotropin, endosialin and an MHC Class II protein.

26. The kit of claim 24, wherein said targeting antibody, or antigen-binding fragment thereof, binds to a surface-localized component of intratumoral vasculature selected from the group consisting of VEGF/VPF, FGF, TGFβ, a ligand that binds to a TIE, a tumor-associated fibronectin isoform, scatter factor/hepatocyte growth factor (HGF), platelet factor 4 (PF4), PDGF and TIMP.

27. The kit of claim 23, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to a cytotoxic agent.

28. The kit of claim 23, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to a coagulation factor or to an antibody, or antigen-binding fragment thereof, that binds to a coagulation factor.

29. The kit of claim 23, wherein said targeting antibody, or antigen-binding fragment thereof, is operatively linked to deglycosylated ricin A chain, Tissue Factor, truncated Tissue Factor or to an antibody, or antigen-binding fragment thereof, that binds to Tissue Factor or truncated Tissue Factor.

30. (Amended) The kit of claim 1, wherein said kit comprises biologically effective amounts of:

(a) [a] said detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid;

(b) said at least a first [unconjugated] antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid; and

(c) said at least a second anti-cancer agent.

34. (Amended) A therapeutic kit comprising, in at least a first suitable container, a combined pharmaceutically effective amount of at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first unconjugated antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid; and at least a second anti-cancer agent other than said at least a first unconjugated antibody, or antigen-binding fragment thereof.

35. The kit of claim 34, wherein said at least a second anti-cancer agent is an anti-angiogenic agent, apoptosis-inducing agent or a vascular targeting agent.

36. The kit of claim 34, wherein said kit further comprises a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid.

37. A medicinal cocktail comprising, in a pharmaceutically acceptable form, a combined effective amount of at least a first anti-cancer agent and at least a first unconjugated antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid.

38. (Amended) In combination, biologically effective amounts of:

(a) a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid;

(b) at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first unconjugated antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid; and

(c) at least a second anti-cancer agent other than said at least a first antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid.

39. A kit comprising at least a first antibody that binds to an aminophospholipid on the luminal surface of tumor vascular endothelial cells in an amount effective to kill at least a portion of said tumor vascular endothelial cells upon administration to an animal with a vascularized tumor; said kit further comprising:

(a) a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid; or

(b) an anti-cancer agent.

40. A kit comprising at least a first antibody that binds to an aminophospholipid on the luminal surface of tumor vascular endothelial cells in an amount effective to induce cell death in at least a portion of said tumor vascular endothelial cells upon administration to an animal with a vascularized tumor; said kit further comprising:

(a) a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid; or

(b) a therapeutically effective amount of an anti-cancer agent.

41. A kit comprising at least a first antibody that binds to an aminophospholipid on the luminal surface of tumor vascular endothelial cells in an amount effective to effective to occlude or destroy at least a portion of tumor blood vessels upon administration to an animal with a vascularized tumor; said kit further comprising:

(a) a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding region thereof, that binds to an aminophospholipid; or

(b) a therapeutically effective amount of an anti-cancer agent.

42. A kit comprising at least a first antibody that binds to an aminophospholipid on the luminal surface of tumor vascular endothelial cells in an amount effective to induce tumor necrosis, tumor regression or tumor destruction upon administration to an animal with a vascularized tumor; said kit further comprising:

(a) a diagnostically effective amount of a detectably-labeled antibody, or antigen-binding region thereof, that binds to an aminophospholipid; or

(b) a therapeutically effective amount of an anti-cancer agent.

43. (New) The kit of claim 1, wherein said at least a first pharmaceutically acceptable formulation is a liposomal formulation.